TuberXpert: Clinical Decision Support System for anti-tuberculosis medical drugs

SPIRIT SNSF project proposal by:

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1 Summary

Background: Tanzania has a high burden of Tuberculosis (TB). In 2018, the country estimated 142'000 new TB cases. The country is also facing the challenges posed by TB/HIV coinfection and an emerging TB/diabetes mellitus (DM) epidemic. Treatment of TB/HIV and TB/DM patients is complicated, with a considerable proportion of cases ending with unfavorable outcomes including treatment failure, relapse, and death. Unfavorable treatment outcomes are largely driven by both incomplete observance and pharmacokinetic variability of first line antitubercular (anti-TB) drugs, subsequently leading to insufficient circulating drug exposure and development of drug resistant TB, or to excessive exposure and toxicity leading to treatment interruption. The global community, through the END TB strategy [1], has declared its willingness to end TB by 2035, and a central component of the arsenal for this includes resorting to the correct use of anti-TB drugs, in particular the first-line agents: isoniazid, rifampicin, ethambutol and pyrazinamide. Precision dosage of medicines based on drug concentration monitoring is an important patient-centered approach for optimizing observance and efficacy and preventing adverse effects. Such a process can take advantage of software tools like Tucuxi [2] [3] – a software already developed by HEIG-VD and CHUV – that will be used as the core computing component for the interpretation of drug concentration results and consequential dosage optimization.

Aims and objectives: We will develop an automated Clinical Decision Support System (CDSS) to help practitioners with the dosage adaptation of rifampicin, one of the essential medical drugs targeting TB, known for large pharmacokinetic variability and frequent suboptimal blood exposure. Such an advanced system will encourage the spread of a dosage-individualization culture, including among practitioners not specialized in pharmacology. We will give particular attention to the design of the measurement and interpretation report, so to fit the final users' needs. The software, in order to predict correctly drug concentrations and to propose meaningful adjustments, requires an embedded pharmacokinetic model for rifampicin. Thus, the objectives of this project are to: (1) in a first step, develop the appropriate population pharmacokinetic (popPK) model for rifampicin for Tanzanian patients and implement it within Tucuxi; (2) optimize the reporting of relevant information to practitioners for drug dosage adjustment; (3) automate the delivery of the report in line with the measurement of drug concentration [4]; (4) validate and implement the final system in the field.

Methods: The three teams will combine their efforts to deliver the first automated Therapeutic Drug Monitoring (TDM) CDSS for TB. A study, led by Kibong'oto Infectious Diseases Hospital (KIDH), involving final users in Tanzania, will help organizing the information required as well as devising the best way to represent it. It will consist of interviews where mock reports will be shown to participants to identify the most required items. In parallel, a rifampicin popPK model will be developed taking advantages of (a) the published literature, complemented with (b) data provided by a study already planned in Tanzania and (c) samples collected within this project. This model will then be implemented within the Tucuxi framework by CHUV and HEIG-VD. The automated report generation will be developed by HEIG-VD and validated through selected case studies by CHUV and KIDH. Finally, the KIDH team will validate the generated report by confronting the dosage adjustments with decisions of clinicians in the field, within a prospective study comparing the adjusted utilization of rifampicin with its traditional prescription during the control period.

Expected results: At the end of the TuberXpert project, Tanzania will possess a new tool to help the practitioners with the adaptation of drug dosage targeting complicated TB cases (TB/HIV, TB/DM, TB/malnutrition). This automated system will be validated and used in the field, and the system will be proposed to other countries affected by endemic TB. In addition, this approach will serve as proof of concept regarding the feasibility and suitability of TDM for further anti-TB drugs, in particular second-line treatments considered important to monitor. It will also be fairly straightforward to extend the software's capabilities to other drugs, which will help improve the management of neglected diseases by making the most of TDM.

2 Research plan

2.1 Current state of research in the field

Over the last decade, Tanzanian health authorities estimate an incidence of 120'000-150'000 patients per year for TB, while no more than 60'000–75'000 patients are notified and receive a treatment. A high prevalence of insufficient dosage of rifampicin, resulting in low rifampicin concentration, has been reported during studies in Tanzania and elsewhere [5]. For example, investigations by Heysell et al. (2011) and Tostmann et al. (2013) in the Kilimanjaro region showed that one to two thirds of uncomplicated TB patients had maximum concentrations below the reference range of 8-24 mg/L, defined two hours after last dose intake [6] [7]. A considerable proportion of individuals with TB are coinfected with HIV, representing 25–40% in surveillance reports. In such patients, Semvua et al. (2013) found that co-administering antiretroviral drugs with first line antitubercular (anti-TB) drugs further lowered rifampicin concentration [8]. This predisposes them to a definite risk of treatment failure or unfavorable outcome.

Simultaneously, the country observes an increase of diabetes mellitus (DM) prevalence among TB patients, representing 4–16% in rural and urban settings [9] [10]. DM may alter the pharmacokinetics (PK) of various drugs including anti-TB [11], as illustrated by Mtabho et al. (2019) who observed that DM independently predicted low levels of rifampicin in TB Tanzanian patients [12]. Established evidence in Tanzania shows that individuals with a coexisting TB and DM condition have a 5-fold risk of death compared to those without DM [13].

Recently, clinical trials are being conducted in Tanzania and elsewhere for optimizing rifampicin dosage in uncomplicated TB; however, the clinical trials pathway takes a long time to reach individuals with TB and other comorbidities such as HIV or DM [14].

One of the promising TB clinical trials in uncomplicated TB patients conducted in Tanzania and South Africa provided more evidence regarding the PK variability of rifampicin in two different populations [15]. In average, Tanzanian patients had a substantially lower drug exposure than South African patients [15]. This emphasizes the limits of "one-size-fits-all" dosage recommendation strategy, hence calling for a tailored treatment approach. Therefore, the optimization of first line anti-TB drug use to improve their effectiveness makes full sense, in such a resource-limited setting [16]. In that context, Tanzania has designed a health system model that incorporates a component of pragmatic optimization of rifampicin therapy based on drug levels measurement and Therapeutic Drug Monitoring (TDM) [16].

TDM is defined as a procedure to optimize the circulating drug exposure in individual patients through dosage adjustment based on one or multiple drug concentration measurements, so as to reach a certain target defined by appropriate pharmacokinetic/pharmacodynamic (PK/PD) considerations. Its implementation in resource-limited settings having a high burden of infectious diseases such as TB is uncommon [17]. Various challenges hinder the implementation of TDM in resource-limited countries, including unreliable electricity supply, interruptions in cold chains, issues related to distances etc. Despite this, groundbreaking opportunities emerge such as the use of the Dried Blood Spot (DBS) technique that allows for storage and transport of TDM samples at unconditioned temperatures. In Tanzania, we are currently validating TDM assays using DBS for rifampicin, targeting in particular patients with TB/DM. The feasibility study of TDM is nested in a large adaptive diseases control expert programme in Tanzania (ADEPT) [16]. Deploying TDM in routine settings is expected to contribute to the END TB strategy, which targets 90% of treated TB patients be cured [1]. A group of pharmacologists, physicians and relevant stakeholders are working on the clinical standards for TDM that will provide guidance in resource-limited settings to adapt TDM strategies for optimizing TB treatment, with rifampicin as a high priority drug [18]. Integrating a dedicated software in this approach will revolutionize the optimization of rifampicin dosage, particularly in individuals with comorbidities.

Population pharmacokinetic (popPK) approaches employ non-linear mixed-effect modelling to characterize the drug concentration/time profiles (i.e., PK) along with its variability in the studied population, while simultaneously identifying

patient- or treatment-related factors accounting for a defined part of this variability [19] [20]. Once developed, a popPK model informed with observations made on a specific individual allows estimating subject-specific PK parameters, and thus the most probable concentration/time profile expected in this individual, using Bayesian inference. PopPK models are, therefore, the foundations of model-based TDM-guided dosage individualization, usually assisted by software programs because of the required complex calculations. The main advantage of the population approach compared to the traditional methodologies is its ability to work also with few data collected in individuals according to a very flexible time schedule, making it best suited to analyze data collected in real-life patients followed within the frame of TDM programs. On the other hand, a large number of subjects needs to be enrolled in the study to best characterize the drug PK and the associated variability, while identifying influential factors on it. Model-Based Meta-Analysis (MBMA), a recently introduced methodology in popPK, overcomes this limitation by pooling available relevant data together (e.g., literature describing the pharmacokinetic of the drug of interest, together with individual TDM data produced in a target population) to build the best possible model [21] [22]. An MBMA model thus allows describing the drug concentration/time profile and variability in a much larger and diversified population than any included single study, and helps in the identification of clinically relevant factors (i.e., covariates) that might be underrepresented in each of them. Several popPK [23] [24] [25] [26] [27] as well as classic PK [28] [29] or TDM [30] studies of rifampicin have been conducted in TB patients. They assess the impact of a variety of biologically plausible relevant factors (e.g., demographic characteristics such as body weight, gender [30] and age, or comorbidities such as HIV coinfection). This abundant published material eventually makes this drug a suitable candidate for MBMA, thus dispensing with the need for a large-scale study to build up a suitable model. Still, a calibration of the model to the Tanzanian population based on a limited size sample will remain necessary.

TDM, in the clinical practice, requires specific skills and some computation, so as to predict the maximum likelihood drug concentration profile based on the patient covariates, their dosage history, and blood concentration measurements performed. Such computation can be done thanks to either all-purpose spreadsheets like Microsoft Excel (a practice observed in certain institutions) or by specific software applications. Some years ago, we conducted a study that highlighted the lack of suitable software tools to support the medical practice of TDM [31]. The existing solutions were not really appropriate for the daily practice of clinical practitioners. Recently, a new study [32] showed that the world is moving towards more options for so-called Model-Informed Precision Dosing (MIPD) software (MIPD is only one among many terms describing such computer applications). This study compared ten commercial and non-commercial TDM applications by confronting the feedback of 22 experts. Tucuxi was one of the evaluated software, and its graphical user interface was ranked the as the best concerning the report that could be retrieved from an interpretation. All over all, MIPD software are in their early age, and further research and development is to be conducted, as highlighted in January 2021 [33]. While some studies already pinpoint interest in MIPD software for various drugs (imatinib [34] or antibiotics [35] for instance), TDM culture and practice still needs to spread out, notably through education of medical doctors.

Based on this state of research, **this project aims at optimizing and offering such a TDM software tool to clinicians, helping them to make the best adjustments regarding the dosage of anti-TB drugs**. This application will use all information known about the patient, confront it with an appropriate synthesis of the available knowledge on the drug's popPK characteristics, deduce maximum likelihood predictions regarding the result of dosage adjustment, and generate a report containing appropriate information to guide the clinician towards the best dosing decision.

2.2 Current state of own research and partnership aspect

The three applicants (two women and a man) have a long history of research in the domains touched by the TuberXpert project, ranging from daily practice with TB patients to clinical aspects of TDM and efficient software design.

Prof. Stellah Mpagama, based in Kilimanjaro-Tanzania, is currently the lead of the Global South Pan African Consortium for Evaluating Anti-TB Antibiotics (PanACEA), a network encompassing 6 African countries (Gabon, Malawi, Mozambique, South Africa, Uganda and Tanzania) and some European states (including Germany, The Netherlands, and United Kingdom). Stellah Mpagama is also the Director of Research and Innovation at both the national referral hospital for drug-resistant TB and the regional infectious diseases center of excellence (KIDH). She has conducted a wide range of studies, covering basic, clinical and implementation level TB research in Tanzania.

In the last decades, she has actively engaged as the study physician or principal investigator for 5 clinical trials and more than 10 observational studies, and as such, she has an impressive experience in TB research in Tanzania. She serves as the Principal Investigator for a large health system integration of diabetes and TB care named Adaptive Diseases control Expert Programme in Tanzania (ADEPT), sponsored by the Danish Ministry of Foreign Affairs. This program included a component of TDM operational feasibility for optimizing TB/DM clinical management. As part of the TuberXpert project, Stellah Mpagama will serve as Principal Investigator in Tanzania, and she will incorporate it into the ongoing TB/DM program (ADEPT).

Dr Monia Guidi is a well-known scientist with a strong expertise in clinical pharmacokinetics and pharmacometrics in general. Since she joined the Service of Clinical Pharmacology at CHUV in 2010, she worked on the characterization of the PK profiles of drugs in their clinical development phases, as well as those already on the market (e.g., antiretrovirals, antimalarials), by employing both classic PK approaches and more sophisticated pharmacometric techniques (e.g., parametric popPK, MBMA). As senior scientist at the beginning of her career and head of the Pharmacometrics Unit in the last years, she supervised 10 PhD students (mostly women) and is currently co-director of two (a woman and a man) in pharmacometrics. The research of Monia Guidi focuses on the clinical applications of the developed popPK models and, in particular, on therapeutic individualization and optimization in special populations. For example, she participates to the OPTAT (OPtimizing oral Targeted Anticancer Therapies) study that aims at optimizing the therapeutic use of protein kinase inhibitors in cancer patients through a popPK approach [36]. In addition, she applied modeling and simulations methods to data collected in African children after administration of a fixed dose resulting from the combination of two antimalarial drugs, to support the dosing recommendations for this new combination therapy (study performed in collaboration with the not-for-profit organization DND*i* [37]). She also contributed to the SwissPedDose project with the analysis of the antibiotics vancomycin [38] and imipenem [39]. In these studies, data collected in premature neonates allowed the identification of the best dosage regimens, i.e., those associated with optimal therapeutic effect while minimizing secondary effects, as a function of specific patients' characteristics. The vancomycin model is currently implemented in Tucuxi to assist the pharmacologist in determining the right dosage regimen (i.e., therapy individualization) for neonates hospitalized at CHUV. Recently, her team applied the MBMA approach to a doping agent in a project sponsored by the World Anti-Doping Agency (WADA). Such analysis allowed modifying the existing WADA recommendations on the daily administration schedule to better discriminate between doping and therapeutic use of the investigated drug [40]. Of course, the development of strong collaborations with different stakeholders (i.e., pharmacologists, TDM and analytical methods experts, and clinicians involved in patient's care) are essential for the success of all these projects.

Prof. Yann Thoma, is a well-known researcher focusing on biomedical applications and acceleration of data processing. He participated to the ISyPeM2 nano-tera.ch project where, in collaboration with Prof Thierry Buclin (head of the Service of Clinical Pharmacology at CHUV), he developed the Tucuxi system [2], a software helping pharmacologists to interpret drug concentration measurements and to adapt dosages. Currently he collaborates with various research groups

(University of Sydney, Royal Prince Alfred Hospital (Syndey), CHU Lyon, Vall d'Hebron hospital (Barcelona), CHUV), to clinically validate this software or to use it as a tool for pharmacological studies. For instance, Tucuxi has been used in a study [41] about tobramycin and the relevance of a single *vs* two measures for TDM. It has also been used in a comparative study [42] in which three different popPK models for vancomycin were compared. On the more general side of data processing for biomedical applications, Yann Thoma has been working on neuronal spike detection [43], and on the processing of genomic data thanks to specialized hardware [44] [45] [46].

Considering Tucuxi, from its initial development, various refactoring allowed this software to become a stable and mature source code. Its architecture is highly modular, and offers a computing core that can be embedded within a Graphical User Interface (GUI), a REST server, a Command Line Interface, or any new software. The current GUI offers to practitioners an easy-to-use tool to help with the interpretation of drug blood measurement results. However, its use still requires some pharmacological skills that general practitioners infrequently possess. Enabling TDM for TB patients would therefore require some additional assistance to be given to the physicians, in order to spread this technique across Tanzania.

In its current state, the computing core (which will be used within TuberXpert) is able to perform the following operations: (1) prediction of drug concentration, based on the patient's covariates and drug blood concentration measurements, (2) percentiles calculation based on patient's covariates or on patient's covariates and actual measures, (3) proposition of dosage adaptations to reach the therapeutic targets. Pharmacokinetic mathematical models (e.g., linear elimination with 1, 2 or 3 compartments, Erlang-type absorption, …) are embedded into the source code, and drug models (using the mathematical models, but defining their parameters) are supplied thanks to external files, allowing the users to implement new models without software programming knowledge. This core-computing module has been verified in detail, thanks to unit and system tests, and is fully functional. Its purpose is purely to perform computations, not to evaluate measurements accuracy or take any decision about potential new dosages. As such, it will be one of the building blocks of this project, letting the new Clinical Decision Support System (CDSS) exploit its capabilities. The current GUI can be used by manually entering data, but can also be connected to an external database by means of HL7 data exchange [47] [48], a standard for connectivity in the medical field. This feature will be valuable to potentially connect our CDSS as a service in an eHealth system to autonomously create reports that could help the practitioners.

In terms of existing collaborations, Monia Guidi and Yann Thoma have been working on Tucuxi for several years. Monia Guidi had the opportunity to supervise various Master Thesis and PhD students that implemented new drug models into the software and validated them (e.g., the antiretroviral drugs darunavir by Dr Catalina Barcelo and doravirine by Dr Perrine Courlet, the antibiotics vancomycin in adults and neonates by Julien Massari and Dr Kim Dao, respectively, and meropenem by Wongsathorn Citino). In that context, Yann Thoma offered support to the students during the model writing and the automatic validation of these new models while Monia Guidi focused on the popPK models development/selection.

Stellah Mpagama is currently involved in the ADEPT project, funded by the Ministry of Foreign Affairs of Denmark under the Danish International Development Agency, in which Tucuxi will be used for the validation of rifampicin dosage in patients with both TB and DM condition. Yann Thoma is therefore involved in the adaptation of the software to embed a new popPK model based on the existing literature [27]. This fruitful collaboration is a first step towards rifampicin TDM for patients with a coexisting TB and DM condition in Tanzania. It is to be noted that the TuberXpert project goes far beyond this first collaborative step. The model that has been implemented will be more thoroughly evaluated and challenged against other identified model candidates, thanks to the CHUV expertise, and will likely be replaced by a newly developed MBMA model. Also, we will take advantage of blood samples collected during both the ADEPT and the current projects to refine the selected model and calibrate it to the target population where it is to be used.

The three applicants, together with their respective teams, fully cover the spectrum of competences required for the success of the project. Three PhD students will be hired and will closely collaborate to develop the best solution for helping with TB treatments adaptation supported by CDSS.

Stellah Mpagama and her team will have access to the field practitioners, as well as to patients with both TB and DM. They will collect specimens for TDM and analyze them at the Biotechnology laboratory in Kilimanjaro - Tanzania. Their involvement in TB treatment will bring invaluable insight to the project, and allow a wide spread of the results among the medical doctors in Tanzania. Monia Guidi and her team will provide all the expertise required for the pharmacometric analyses, including meta-analysis of existing data, together with the CHUV pharmacologists' experience. They are indeed involved in the clinical interpretation of more than 5'000 drug measurement results interpretations per year for some 120 different drugs, and as such they can be considered as a group of strong expertise in TDM. Confronting their view about the reports design with the view of Tanzanian doctors will surely be highly valuable. Yann Thoma and his team will bring all the software skills required for the development of the CDSS, notably in terms of reliability. The years of Tucuxi development allowed his team to gain a deep knowledge in pharmacology, definitely required to both understand the final users' needs and to develop valuable and reliable software for pharmacologists and medical doctors.

2.3 Detailed outline of planned research

This interdisciplinary research project involves five main axes: (1) PopPK models selection/development, elaboration and validation/calibration with Tanzania patients, including update of the core computing software; (2) Definition of the information to be supplied to the clinicians to support dosage adjustments, as well as definition of the most accurate visual way of presenting it; (3) Realization of a CDSS as an automated report generator based on the adapted core computing engine for drug concentration prediction based on measured values; (4) Validation of the generated reports by expert pharmacologists; (5) Implementation of the tool in the field during a prospective study to assess the feasibility and the advantages of its use by clinicians in Tanzania. The first three axes will converge into the final software, and the validation/implementation phases will allow assessing the correctness and usefulness of the adjustment suggestions.

Model selection, development and calibration

The selection of the popPK model to implement in Tucuxi is crucial in this project, as it determines the ability of the software to propose the right dose for each patient. An extensive literature search will be conducted to identify the published popPK models of rifampicin in TB patients [49], [24], [50], developed using NONMEM [51] or Monolix [52], both widely used computer programs for popPK. As previously mentioned, DB and HIV are comorbidities often present in TB patients, and thus will consequently be investigated as influential factors on anti-TB drugs PK. The number of participants in the studies, as well as that of available observations distributed over time, will be taken into account. The description of the model development steps (e.g., structural and statistical considerations, inclusion of covariates) will be carefully reviewed, and the study results will be judged using standard procedures in population analysis (e.g., diagnostic goodness-of-fit plots, type of validation) to ensure the quality of the model and the completeness of the information provided. The available models will be ranked according to a cumulative score based on the previous elements and the best one will be selected for implementation. As already mentioned, and in case no single model can be identified as best one, an MBMA approach will be used to build a comprehensive popPK model using all available pertinent literature. Because of the auto induction and the non-linear processes underlying rifampicin absorption and elimination, we do expect a complex non-linear popPK model to best characterize its PK (which will require software updates to encompass a specific kinetics). Whatever the choice made for this step, the model will undergo a formal

validation and adjustment to Tanzanian patients using rifampicin concentrations collected within ADEPT [53] and the current project, as well as data from CHUV. The TDM program currently implemented in Tanzania as part of the ADEPT project enrolls patients with both TB and DM and fixes two sample collections at 2h and 4h post drug intake for dose adaptation. Sample collection at random times (> 4h post dose) will be additionally performed in 50 TB (including those with HIV co-infection, coexistent DM or malnutrition) patients in the early stage of the TuberXpert project. We will elaborate and then strictly follow a study protocol according to the Tanzania laws for human research for this step by expanding the ADEPT protocol, allowing us to benefit from the same ethical clearance under programmatic settings. All the data collected in Tanzania, together with those of patients followed at CHUV within the frame of the existing routine TDM program, will be used to validate and, if necessary, refine the popPK model in the Tanzanian population. Model validation will be performed assessing the accuracy of model-based precisions. In the case of a significant bias, explanations will be sought and model adjustments will be devised, so that a final model appropriately calibrated to the target population can be offered to practitioners. This calibration step will also offer the possibility of investigating the differences in rifampicin disposition between Tanzania and Switzerland.

Special attention will be devoted to the gender/sex distinction for the model selection. In many of the existing drug models already implemented in Tucuxi, sex is a covariate that affects the PK parameters (currently available Tucuxi models with sex as a covariate and reference to the corresponding published popPK model: apixaban [54], cefepime (not yet published), daptomycin [55], darunavir [56], imatinib [57], tobramycin [58], vancomycin [59] [60] [61] [62] [63]). General evidence exists about drug metabolizing enzyme activity, body composition and kidney function differences between women and men, that might impact drug absorption/distribution/elimination processes [64] [65] [66] [67]. In addition, drug safety and effectiveness might differ according to sex because of the roles of hormones in receptors expression and sensitivity [67]. It is also worth underlying that adverse events and toxicities are more often reported in women than in men, therefore an impact of sex on rifampicin PK or response might be observed. It is to be noted that gender is often mixed with sex in literature. However, a self-defined gender is not expected to influence the PK parameters as specific sex-related enzymes seem to be more important than psychological factors. The hormone therapy, medically necessary to improve quality of life of trans-gender persons, might additionally alter drugs PK and response [66]. Because a popPK study requires a good proportion of individuals with an investigated characteristics to detect its significance, gender differences non-correlated to sex will be hard to observe, while sex will likely be a potential covariate. We will, however, do our best to get information about the gender and the sex of the patients used in our study. Concerning our study, we will take care of having a good ratio of men and women patients. It will require a special attention, as in the population of TB patients a ratio of 2 men for 1 women is currently observed.

In Tucuxi, drug concentration predictions can be computed (1) without any knowledge about the patient, (2) with consideration to patient's covariates, or (3) knowing both patient's covariates and drug concentration results in blood. In the first context, the computations are done for the so-called "typical patient". Interestingly, the pharmacologists often consider this typical patient to be a male of 50 years old and 70 kg. If not all covariates are known for a specific patient, these typical values are used as they are the best guess. Obviously, concerning sex, the best guess is to consider the person as being in-between female and male. This is exactly how we will manage the rifampicin model built during the project. In case the sex information is unknown, then we will consider the influence of sex being the average of female and male influences. This way of treating this covariate will allow to get rid of the frequent bias observed in standard clinical practice.

In addition to differences in PK parameters between individuals (i.e., Inter-Individual Variability (IIV)), a popPK model allows describing the PK variations within the same individual at the PK parameters level using an Inter-Occasion Variability (IOV), and at the observations level using residual non-explained variability, that encompasses analytical errors, uncertainty in sampling/administration times as well as model misspecification. Inclusion of IOV is possible

whenever each individual contributes with PK observations on different occasions, e.g., visits, and its management for individual parameter estimation through Bayesian inference is not trivial [68]. Several recently published simulation studies investigated the best way to handle IOV for dose forecasting in parametric MIPD software [69] [70]. They compared dose and individual PK parameters obtained with the original model containing IIV and IOV *vs* dose predicted with only IIV but using PK parameters with and without the IOV term, with a new IIV obtained as the sum of the variances of the two original variabilities or re-estimated from the original dataset ignoring the IOV term. The authors concluded that the best strategy for model-based TDM is to include IOV in parameters estimations while neglecting it for dose forecasting of the next occasion. This is valid also for drugs characterized by high IOV – and thus for rifampicin – for whom an important variation in PK parameters between occasions has been reported [50] [70]. Interestingly, samplings collected in two occasions appeared to be enough to capture IOV and thus predict the optimal dose at the next occasion in the in silico study for rifampicin [70]. It is most likely that the chosen popPK model for rifampicin, either among those published in literature or developed using an MBMA approach and extended/validated to depict the available Tanzanian and Swiss data, will have IOV components, in addition to non-linearity in the absorption and elimination phases as previously mentioned. However, the current computing component of Tucuxi does not take IOV into account, and, as such, a model with IOV has to be truncated in order to fit within the software. Therefore, in order to get the best out of potential rifampicin models, the source code will have to be adapted. As presented above, some choices have to be done about the best way to manage IOV for the various computations (predictions, percentiles, dosage adaptations). Also, the non-linearity of rifampicin in the currently published popPK models will likely imply the addition of new PK models within the source code. The new code, both for IOV and non-linear PK models, will have to go through a verification process to ensure all computations are fully reliable.

Model validation

The calculations made by Tucuxi have to be validated against the gold-standard software for popPK analyses, i.e., NONMEM, prior to any use of the software in clinical patient management. This step will be performed thanks to a cross-validation of the developed popPK model implemented in NONMEM and in Tucuxi. Both implementations will be carried on by different people (a person at CHUV and another one at HEIG-VD), so to minimize the risks of errors. Simulations will be conducted in this intent using standard procedures in NONMEM and compared to the Tucuxi calculations. If the results do not equal each other, then the model developers will have to agree on the right way of implementing it in the different software. Finally, Monia Guidi and Yann Thoma will conduct a review of the implementations to find any remaining potential issue.

A further essential preliminary validation step for the successful use of Tucuxi in therapy individualization is to ensure that the dosage regimen propositions made by the software are in agreement with those of experienced pharmacologists used to perform TDM in their clinical practice. The Service of Clinical Pharmacology of CHUV and KIDH will be in charge of such clinical validation of the software using selected patients of the ADEPT study. KIDH will provide data on rifampicin dosage history and concentrations, with administration and sampling times, as well as all necessary clinical information on the selected patients. An experienced pharmacologist will select the most appropriate dosage regimen to achieve the target according to the patient clinical status among those proposed by the software using the Graphical User Interface of Tucuxi. The correctness of the forecasted dosing schedule will be validated against the dosage recommendations made by the TDM experts at CHUV and KIDH in standard practice. After this important validation step, the model will be made available within the standalone Tucuxi software, allowing users to exploit this new model.

Report specification

Reports generation, and specifically the report structure and visual content, is of first importance to help clinicians with decision-making. It shall be easily understandable by non-pharmacologists. The information to be displayed needs to be carefully selected and structured, so to not lose the prescriber with a too complex presentation and terminology [71].

It should contain the appropriate information, presented in a visual way. In addition, alerts shall be issued if necessary in a way following the I-MeDeSa principles [72]. Special attention will be given to appropriate corrective actions [73]. For instance, if a measured drug level appears out of range, an alert shall clearly identify either a potential error in the data or a lack of observance whenever such sources of bias can be identified with sufficient certainty. In less clear situations, an estimation of the likelihood of common artifacts *vs* a definite individual PK alteration in the patient should be issued. The definition of the report layout will be elaborated through the following process. We will identify common and uncommon use cases (e.g., type of patient, under/over drug exposure, standard/strange observed drug level). The TB patients treated in Switzerland are usually special cases compared to the daily routine of TB patients in Tanzania. Therefore, the use cases selection from both countries will offer an extremely interesting variability. We will also design artificial use cases, to cover as many borderline cases as possible. Based on these use cases, we will design mock reports showing various layouts. The designs will be done by closely interacting with two expert pharmacologists (at CHUV) and two general practitioners (at KIDH) to guide the design into a direction relevant for the final users. We will then, in Tanzania, expose a cohort of clinicians to these reports and collect their input through a carefully designed form. We expect to reach 10 facilities, with 2-3 persons per facility. As already identified by KIDH, we expected to reach a ratio of 50-50 female-male practitioners. This will avoid any gender-based bias within the study, but will also allow us to identify such bias by linking the analysis results with the practitioner gender. We will also target European clinicians through the same study to get useful information about cultural biases in terms of information representation. Finally, we will also target European pharmacologists to get an understanding of their specific needs compared to general medical doctors. We will improve the rendering of the report over the necessary number of cycles, with thorough attention to the clinicians' feedback. The output of this study will allow designing the final report. This study will also allow illustrating the differences between pharmacologists and general medical doctors, between Europe and Tanzania, and potentially between female and male practitioners for reports acceptance.

Clinical Decision Support System

Tucuxi is a software that helps a clinician to adapt dosages for medical drugs. It offers a graphical user interface, graphs with drug concentration predictions surrounded by percentiles, and dosage adaptation propositions. The computations are based on the patient's covariates, potential drug concentration measurements, and on the popPK models implemented within the software, as well as PK targets validated by TDM experts for dose optimization. Specifically, it uses Bayesian inference to find the most likely individual parameters integrating information from both the underlying model and the observations obtained on the patient. Currently, the user has to take decisions by himself/herself, as well as to write some sentences to fill up a report. This manual job is done by experienced pharmacologists, as it requires specific skills related to this specialized medical discipline. Clinicians who make final decisions about the drug dosage usually do not have these competences, and as such rely on monographs, experience, or a consultation with a pharmacologist. In that context, a CDSS can bring much information for decision makers [74] in locations where expert pharmacologists are not easily available.

The CDSS that will be developed will offer various features: (1) assess the expectedness (likelihood) of a drug concentration result, taking into account the patient's characteristics; (2) assess the adequateness (target attainment) of the current dosage; (3) propose a dosage adjustment if required; (4) present clear and meaningful messages within the report to help the clinician with the decision making process; and (5) generate alerts when data seems suspicious or erroneous.

While the current Tucuxi software allows performing the necessary computations, except IOV and potential missing PK models (as stated in the previous section), it will need to add a new level on top of the computing engine. Research is necessary to ensure that the system is extensible enough to address other medical drugs without huge refactoring. Therefore, a perfect balance between genericity and TB/rifampicin-specific features has to be found. The system will

also have to be easily integrated into existing systems thanks to a generic interface. It will also need to be extremely reliable and deployable in the field.

We will exploit the use cases defined within the report specification phase to write specifications of the CDSS. We will carefully analyze every single case to design a formal decision tree [75] that will lead to the software development. This decision tree will be required to design the software and will also be published as a relevant guide for clinicians that are doing the job by hand.

The report to be generated shall not only display useful values and graphs, but shall also offer readable sentences. In close relation with the decision tree, a set of standard customizable sentences will have to be defined. They will then serve to generate medically meaningful reports, as if they had been written by a human professional. Obviously, these sentences will be related to TB and rifampicin, but the software will be developed keeping in mind that it should be straightforward to define new sentences for other diseases and medicinal drugs. The core components will be generic, and a parametrization thanks to some configurations will allow repurposing to be done as easily as possible.

In terms of software architecture, we will separate the CDSS from the report generation, the CDSS offering a standardized output (most probably in XML format). In our case, this output will be used by the report generator to fill some fields of a report template. Introducing such separation of concerns will ease the verification of the CDSS and will offer potential future integrations within electronic health systems. The interface of both software parts will therefore have a common interface allowing their integration within various frameworks (command line interface, web front-end, an existing eHealth system). In particular, we will ensure that it can be connected to the laboratory information system that manages the transmission of drug concentration measurement results. Also, having a version of the CDSS where computations are running remotely could be an option if the clinicians in the field do not own computers with enough computing power. In case this approach is required, the patient's personal data could stay on the clinician's computer to ensure data privacy.

Currently, other drugs used for TB treatments (isoniazid, ethambutol and pyrazinamide) are not common candidates to TDM. However, TDM tends to be increasingly recommended, in particular for the treatment of multidrug-resistant TB with second-line chemotherapeutic agents, when the achievement of effective and safe concentration exposure is of vital importance [76]. If future research projects end up with popPK models, or if enough observations are collected in Tanzania and CHUV, TuberXpert could be adapted beyond this project to embrace them. More generally, as TDM holds promise far beyond the field of tuberculosis alone, this project could have definite indirect benefits in other therapeutic areas such as HIV, cancer etc.

System validation

Validation of TuberXpert will then be conducted after completion of the CDSS/report generation, and taking into account that the rifampicin popPK model has already been validated and calibrated to the target population. We will assess the correctness of the generated reports based on use cases that will be designed within the project among patients under rifampicin that are followed at CHUV and on the data gathered in Tanzania during the ADEPT and TuberXpert projects (15 patients from CHUV, and 25 from both ADEPT and TuberXpert, i.e., randomly selected 50% among hospital/study patients). As previously observed, the CHUV patients present often a very complex clinical situation allowing for report generation testing also in extraordinary cases. Experienced pharmacologists will generate a manual report using the GUI of Tucuxi to individualize the therapy of the selected patients. Such "standard" document will contain all the essential information to justify the selected dosage adjustment, including patient clinical situation, data non-reliability or inconsistencies, and will serve as gold standard for the TuberXpert report. We will verify the correctness of the provided guidance together with the presence of all the necessary clinical information, justifications and warnings. We will confront the manual reports and the ones generated by TuberXpert to identify any discrepancy. This step will also allow for the refinement of the report so to guarantee the reliability of the information for the final user, i.e., a clinician without strong

TDM expertise. Before conducting this validation, we will elaborate a detailed protocol, as there is some kind of subjectivity in the analysis of a specific patient by a practitioner.

After this first validation step, we will update the CDSS and the report generation, based on the study results and specifically on the feedback of the pharmacologists. Indeed, the CDSS development will be driven by the use cases defined at the project beginning, while the validation will be conducted on a set of retrospective data. As such, it is very likely that some adjustments will be required.

After the software update, we will conduct a second validation, following the same protocol but on another set of patients (the remaining 25 from ADEPT, 25 from the current project, and 15 from CHUV). This second step should end with very few differences between the pharmacologists' outputs and the generated reports, and we only expect minor modifications of the software to be necessary after that. Finally, we will again run TuberXpert against all the use cases to validate it against the pharmacologists choices made during the two validation steps.

Implementation in the field

The last project phase consists in the CDSS implementation in the field and a prospective study following a strict protocol that will be elaborated according to Tanzania laws on human research. As in the first project step, the ethical clearance of the ADEPT project will be expanded to embrace this study. The goal will be to observe the relevance of the generated reports for the clinicians in Tanzania. KIDH will select a cohort of clinicians actively involved in TB treatment with rifampicin that in turn will identify patients to enroll in the study. This step will allow assessing the benefit of a CDSS use versus a practice without such help. Thanks to the existing network of KIDH, we expect to have at least 30 patients in the cohort, treated in 10 facilities in the field. We will ensure to embed a fair balance of women and men, both in the patients cohort and in the clinicians participating to the study.

Before introducing TuberXpert to the clinicians, we will ask the selected panel to follow their patients according to standard clinical management while collecting all the needed information for a TDM procedure. We will record the possible dosage adjustments, the patient's health status evolution (i.e. clinical features and pragmatic microbiology parameters), and all the data available about the patients. The KIDH PhD will use the latter information to feed the CDSS so to determine if the clinicians did take decisions corresponding to the CDSS output. This CDSS usage will be done without interfering with the patient treatment.

Then we will train the clinicians about the use of the CDSS and the report interpretation. A Swiss delegation will go to Tanzania in order to do this in the field. This training will not only be beneficial for the current project, but also for spreading the TDM culture throughout Tanzania.

After the training session, we will set up the CDSS in the clinics participating to the study. We will also set up a communication channel with the Swiss team, to help the clinicians with any question regarding the software usage or TDM in general. The clinicians will be the same as in the previous non-CDSS phase. If possible, we will try to reach more of them, as the participation to the first phase is not mandatory to be part of the second one. The study protocol will be written during the project, and will put a strong emphasis on the clinical relevance of the CDSS as well as on the acceptance of the software tool [77]. The clinicians will be asked to collect the same information as in the first implementation phase, including clinical features during the patients' follow up and pragmatic microbiology parameters. Likewise, we will establish the baseline information of safety of TDM through observing and assessing patients' clinical evolution between the two phases, which will subsequently offer the opportunity to assess the overall benefit of the CDSS-assisted *vs* standard patient management in Tanzania. This second part will also help to identify the cases where the clinicians have been influenced by TuberXpert, the reason why they would not be keen to follow the suggested regimens, and if the outcome of the dosage adjustment has been positive for the patient. If the CDSS suggestions are scarcely followed by clinicians, we will investigate the barriers and bottlenecks that hinder its application strategies to increase the accessibility of benefit of TuberXpert technology. The analysis will be then performed comparing the

subgroup of clinicians that followed the CDSS recommendations *vs* those reluctant as well as those included in the first phase to assess the CDSS benefits.

Worth noticing, the data collected in the current project will open the opportunity for validation or optimization of *a priori* dosage dose recommendations of rifampicin by studying the relationship between drug exposure and clinical outcome using a population approach.

2.4 Collaboration, work division, schedule, milestones and visits

CHUV will hire a PhD student with a master in medicine, pharmacy, statistics or bioengineering with a strong interest in modeling and simulations of drugs and their applications to improve patients' clinical care. Because of our past experience in this field, we do expect to have mostly female candidates, and, consequently to have a female PhD student working on the development of the popPK model of rifampicin best describing Tanzania data. This person will also work in the implementation of this model in NONMEM, and contribute to the elaboration of the protocols for all the validation steps, including that for the assessment of the benefits of the TDM supported by CDSS *vs* standard practice in Tanzania. The CHUV PhD student will also develop the model to validate/optimize the dosage regimen recommendations of rifampicin to achieve the desired efficacy targets. In addition, at CHUV, clinical pharmacologists (collaborating with Monia Guidi) with a strong expertise in TDM will assist the project for the various validations, and for the refinement/development of the TuberXpert report. At present, the team is equally divided between males and females, situation that is not expected to change in the next years.

HEIG-VD will hire a PhD student with a background in software programming and/or bio-engineering showing a strong interest in the pharmacology field. We potentially expect a person with a computer science degree, where there is definitely a strong bias towards men students, or coming out of a bioengineering master at EPFL, where 50% of students are female engineers. In case of a final set of candidates with equal skills, we will favor the woman candidate. This PhD student will work on the Tucuxi PK model development, the first stages of report requirements, and then on the CDSS. She/he will be in charge of the entire CDSS development and refinement, and will help the KIDH with the deployment of the system in the field. If required, a software engineer at HEIG-VD (collaborating with Yann Thoma) will help with the most complex parts of software design (mainly the integration of IOV capabilities and the required modification to support the expected non-linearity in anti-TB PK, and the interaction with the core computing). This person will be a staff already working at HEIG-VD. While having a female developer at this post would be valuable, unfortunately the team is mainly composed of men (at the time of writing there is only one woman developer for 18 men).

The project will also take advantages of the collaboration with the head of the Center of Research and Innovation in clinical pharmaceutical sciences, prof. Chantal Csajka, who is a UNIL professor already involved in several popPK and Tucuxi projects. With respectively Monia Guidi and Yann Thoma, she will be the co-director of the CHUV and HEIG-VD PhD theses, both students being registered at UNIL.

KIDH will hire a Postdoctoral trainee with a background of bioanalysis showing a strong interest in setting a pharmacokinetics unit in Kilimanjaro-Tanzania. The Postdoctoral will have experience in setting the TDM assays for pragmatic use in TB patients with/without DM, HIV or malnutrition. Likewise, KIDH will hire a PhD student with a medical background who will work with health facilities to ensure that data and specimens are collected according to the protocol and that enrolled TB patients are followed up to capture important safety, tolerability and efficacy of TDM variables. In addition, as Tanzania practitioners will be the final users of the system, the KIDH PhD and postDoc will be responsible for the use cases definitions and for the report requirements. Both the postdoctoral and the PhD student will be supervised by Stellah Mpagama and co-supervised by Yann Thoma and Monia Guidi. They will also work with CHUV and HEIG-VD trainees to ensure the success of the project. Additionally, a field coordinator will be hired by KIDH to communicate with research laboratory and health facilities to ensure that health care providers are knowledgeable and

access results as quick as possible. The field coordinator will also ensure the project data are collected on time. The KIDH TuberXpert team positions will be distributed 50 by 50 to female and male accordingly.

The workplan consists in five work packages (WP). The three teams will closely collaborate on various WPs, but each WP and task will have a person responsible for it. KIDH will bring its field knowledge in terms of requirements for clinicians, data availability for the model development, and management of the prospective study. CHUV expertise will be key for the popPK models, from selection to development and refinement to get a final model adjusted to the Tanzanian population, as they already have an in-depth experience with the popPK analysis. They will closely collaborate with HEIG-VD for the implementation of the selected models within Tucuxi, as well as for their validation. Finally, they will also help with the prospective study to validate the newly introduced TDM practice assisted by CDSS in Tanzania. HEIG-VD will be responsible for everything related to the software adaptation and development. As such, they will first participate in the report design and in the Tucuxi adaptation, and will then create the CDSS based on their existing code base. This development will be carefully verified and validated to offer a system as reliable as possible.

In the description of the work packages, we refer to the three PhD students as PhD-C for the one working at CHUV, PhD-H for the one at HEIG-VD, and PhD-K for the one at KIDH. The KIDH postDoc is referenced as PD-K and the field work coordinator as FWC-K. In the column *Personnel* we list the persons involved in the WP, by order of involvement importance.

WP 1	**Rifampicin PopPK model**	Dates	Months 1-18	Personnel	PhD-C, FWC, PhD-K, PhD-H, PD-K

Short Description

In this WP, we will select/develop a popPK model for rifampicin specific for the Tanzanian patients, collect the necessary additional samples for it, and integrate it into Tucuxi.

We will conduct an in-depth literature survey of existing studies providing information on rifampicin PK (e.g., popPK, individual TDM data, and clinical studies). The popPK models will be evaluated to choose the best one. Two PhD students (PhD-C and PhD-H) will do the literature search and the popPK model evaluation/selection independently. In case none of the identified model meets the pre-established evaluation criteria, a meta-model embedding information from all existing relevant literature will be developed. The selected popPK model will be further validated/refined using rifampicin concentrations quantified within the frame of this project and of the ADEPT study to obtain a model well suited to the Tanzanian population. The KIDH team will take care of setting a cohort of 50 TB patients with or without DM, and then of the samples collection without restriction on sampling times. This will guarantee the robustness of the selected model in the prediction of the Tanzanian data.

The integration of the selected model into Tucuxi is likely to require software development (PhD-H), as anti-TB drugs are often characterized by non-linear PK and might include important variations between occasions. We will also develop the drug description files, as well as NONMEM files exposing the same behavior to cross-validate the Tucuxi model implementation against NONMEM thanks to automatic verification scripts. PhD-H will implement the selected model in Tucuxi, and PhD-C will work on the NONMEM description, to confront both implementations.

Objectives

- Identify relevant literature on rifampicin PK
- Develop/select a model
- Integrate/validate the selected model in Tucuxi

Tasks

- Task 1.1: Literature review on rifampicin data
- Task 1.2: Blood samples acquisition in Tanzania
- Task 1.3: PopPK model development based on literature review and blood samples data
- Task 1.4: Integration of the selected model into Tucuxi
- Task 1.5: Validation of Tucuxi model against a NONMEM implementation

Deliverables

- D1.1: Report/article on the existing rifampicin literature relevant for TDM application (M6)
- D1.2: Report/article on the newly developed rifampicin popPK model (M15)
- D1.2: Tucuxi and NONMEM implementations for the selected drug models (M18)
- D1.3: Report on the cross-validation of the models (M18)

WP 2	**Report requirements**	Dates	Months 1-15	Personnel	PhD-K, PD-K, PhD-H, PhD-C

Short Description

The automatic reports generation needs to offer the best reports in terms of content and design, to ease the interpretation task by non-specialists. This WP will therefore consist in a study aiming to identify what information is required to be shown, and how this information has to be offered (text, graphics, underlined, bold, …). First, we will identify useful and representative clinical vignettes that will serve as use cases, both for the reports and for the CDSS design. These vignettes will be manifold: taken from interesting cases of the ADEPT project, from specific past patients at CHUV, and from artificial cases to cover more borderline cases. Then we will create mock reports and let a panel of end users (medical practitioners) indicate what choices are relevant or not. We will select practitioners in Tanzania and in Europe and we will run the study in parallel. We will run several cycles of optimization until a stable version is established, while retouching the report template between cycles. This will allow selecting the best report layout and the relevant information to be shown to the clinicians. The output of this study will be of great interest, not only for the TB-related report generation, but also for other potential medicinal drugs.

The KIDH team will lead the study, but the two Swiss PhDs will also be involved in it (PhD-H for mock reports design, PhD-C for use case definition and the European part of the study).

Objectives

- Identify relevant use cases representative of real patients
- Select the information to be displayed
- Define the final report layout

Tasks

- Task 2.1: Use case definition
- Task 2.2: Design of mock reports
- Task 2.3: Study design
- Task 2.4: Study realization and analysis

Deliverables

- D2.1: Use cases (M6)
- D2.2: Study results (M15)
- D2.3: Optimized report template (M15)

WP 3	CDSS	Dates	Months 6-24	Personnel	PhD-H, PhD-C, PhD-K

Short Description

The first step towards a CDSS is the definition of the decision tree to be used. This design will involve pharmacologists from CHUV, thanks to their knowledge of TDM, and the KIDH team, as they are treating patients in the field, and will be based on the use cases defined in task 2.1. Then we will design and implement the CDSS core, by adding the CDSS layer on top of the existing core computing engine. We will design the core computing in a generic fashion first, to allow further developments for other drugs. Integration of the rifampicin model will then allow specializing some parts of the CDSS that would need to be tailored for that drug. We will add the report generation as a separate module, taking as input the results of the CDSS. It will allow the easy creation of other types of reports rendering in case of future evolutions requiring that. In parallel, we will design the connectivity with the CDSS in a way to easily supply input data and get output results. The input/output format will likely be XML and the interface will first be a pure command line mode, and then potentially as a REST server allowing its remote use. An interface suitable for the Tanzanian clinicians will also be developed to ensure a meaningful use by the clinicians in the field. The final step will be the integration of the software pieces, with rifampicin support, report generation and connectivity.

This WP will mostly be developed by PhD-H, but the other two PhDs will be involved in discussions, mainly during the first phase of decision tree design.

Objectives

- Design and implement a CDSS for automatic TDM interpretation
- Build an automatic report generation exposing the CDSS decisions
- Tailor the system for rifampicin, while keeping as much genericity as possible for further use with other drugs

Tasks

- Task 3.1: Definition of the CDSS decision tree
- Task 3.2: Implementation of the CDSS
- Task 3.3: Implementation of the report generation
- Task 3.4: Implementation of the connectivity and integration of the CDSS and report generation

Deliverables

- D3.1: A decision tree for automatic TDM interpretation that will be published in a scientific journal (M9)
- D3.2: A software system able to automatically generate a report based on the CDSS (M24)

WP 4	System validation	Dates	Months 16-30	Personnel	PhD-C, PhD-H, PhD-K, PD-K

Short Description

The CDSS and the report generation needs to be validated before being used. We will first design a validation protocol. Then, a pharmacologist from CHUV will use the standalone version of Tucuxi to perform TDM interpretations on data acquired from past patients from CHUV and patients enrolled in the ADEPT project, together with patients data acquired in WP1. KIDH will be responsible for selecting interesting cases from the dataset at their disposals. Each interpretation will end with a manually compiled report. In parallel, the CDSS will be used to automatically generate a report. The series of those two reports will be compared to assess the correctness of the CDSS. This process will likely result in software update requirements, to fit the pharmacologist findings. After refinement, a second batch of validation will be performed, following the same protocol, but on another set of data. Finally, a last round of minor software modifications will be applied if required.

PhD-C will be responsible for the validation protocol design, as well as for the validation study (with the help of CHUV staff), the KIDH team will work on the cases selection, and PhD-H will be involved in the software adjustments.

Objectives

- Validate the CDSS and the report generation thanks to the expertise of pharmacologists

Tasks

- Task 4.1: Design the validation protocol
- Task 4.2: First round of validation study
- Task 4.3: Software refinement
- Task 4.4: Second round of validation study
- Task 4.5: Final minor software modifications

Deliverables

- D4.1: A validation protocol (M18)
- D4.2: A report about the two-step validation (M30)

WP 5	**Implementation in the field**	Dates	Months 16-36	Personnel	PhD-K, PD-K, FWC-K, PhD-C, PhD-H

Short Description

The final step of this project consists in a field study involving clinicians in Tanzania. First, a clinical research protocol will have to be designed. Based on this protocol, we will conduct the field study about the usage of the reports generation. The KIDH team will be responsible for setting up a cohort of clinicians to enroll TB patients. Then we will collect data during a phase of standard TB patient management, without reference to the CDSS. A Swiss delegation from CHUV will then go to Tanzania for training Tanzanian clinicians. They will exchange about the basics of rifampicin TDM, to ensure that the reports will be used in a useful manner. PhD-H will also join the trip to help with the setup of the CDSS in the facilities. The clinicians will then conduct the treatments with the help of the CDSS. Data about patients follow up together with choices made by clinicians with and without the use of TuberXpert will be recorded, and the CHUV pharmacologists will share experience with the Tanzanian clinicians about the decision making process. Finally, we will analyze the study results, including the analysis of the relationship between rifampicin exposure and clinical outcome to make new dosage recommendations.

The KIDH team will be responsible for all the field activities, while PhD-H will offer support for the CDSS use and the CHUV team will participate to the study design, the clinicians training, and the study analysis.

Objectives

- Give Tanzanian clinicians a better insight about TDM of rifampicin
- Validate the system use thanks to a field study

Tasks

- Task 5.1: Protocol design of the field study
- Task 5.2: Standard patient management in the field
- Task 5.3: Training of Tanzanian clinicians
- Task 5.4: CDSS-assisted patient management in the field
- Task 5.5: Study analysis

Deliverables

- D5.1: A protocol for the field study (M18)
- D5.2: A clinical study report analyzing the field study in details (M36)

Four milestones will pave the way to a successful CDSS for anti-TB drugs dosage adjustments:

Milestone	Month	End of task	Description
M1	15	T2.4	Definition of the reports content/layout
M2	18	T1.5	Elaboration, validation and implementation of a popPK model for rifampicin for Tanzania within Tucuxi
M3	30	T4.5	A CDSS with automatic report generation validated by expert pharmacologists
M4	36	T5.5	System validation and implementation in field conditions

The following Gantt diagram presents the project schedule, and highlights the four milestones as well as the partner responsible for each WP and task. Many tasks will involve more than one institution, but we opted for conciseness in this diagram.

			Year 1				Year 2				Year 3			
WP/ task	Title	Resp. institution	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
WP0	**Management**	**HEIG-VD**												
WP1	**Rifampicin popPK model**	**CHUV**												
T1.1	Literature review	CHUV												
T1.2	Blood samples acquisition	KIDH												
T1.3	popPK model development	CHUV												
T1.4	Tucuxi drug model development	HEIG-VD												
T1.5	Model validation	CHUV						M2						
WP2	**Report requirements**	**KIDH**												
T2.1	Use case design	KIDH												
T2.2	Design of mock reports	KIDH												
T2.3	Report study design	KIDH												
T2.4	Report study realization and analysis	KIDH					M1							
WP3	**CDSS**	**HEIG-VD**												
T3.1	Definition of the decision tree	HEIG-VD												
T3.2	CDSS implementation	HEIG-VD												
T3.3	Report generation	HEIG-VD												
T3.4	Connectivity and integration	HEIG-VD												
WP4	**System validation**	**CHUV**												
T4.1	Design of the validation protocol	CHUV												
T4.2	First round of validation study	CHUV												
T4.3	Software refinement	HEIG-VD												
T4.4	Second round of validation study	CHUV												
T4.5	Final software refinement	HEIG-VD										M3		
WP5	**In the field implementation**	**KIDH**												
T5.1	Protocol design of the field study	KIDH												
T5.2	Standard patient management	KIDH												
T5.3	Training of Tanzanian clinicians	CHUV												
T5.4	CDSS-assisted patient management	KIDH												
T5.5	Study analysis	KIDH												M4

Thanks to technology, the collaboration will take advantage of regular remote meetings. For each work package, the manager will take care of setting up monthly meetings, and for each task, the task manager will have weekly meetings with the persons involved. We are aware that the travel prices are not prohibitive (400-900 CHFs for a 2-way ticket), but that the trip duration ranges between 12 and 18 hours. Therefore, the following visits are envisioned (and budgeted):

Month	Duration	Nb. people	Location	Purpose
1	2 days	4	Tanzania	Kickoff meeting, to meet in person before further remote meetings. It will allow the Swiss participants (two persons from CHUV: PhD + Monia Guidi, two persons from HEIG-VD: PhD + Yann Thoma) to get a better understanding of the facilities found in Tanzania.
6	1 week	3	Switzerland	The PhD student and postdoc of KIDH will come to Switzerland to closely interact with the CHUV team, in order to get familiar with the current version of Tucuxi and gain insight of the way TDM is done in Switzerland. Stellah Mpagama will also join the team, but only for meetings on 2 days.
18	2 days	3	Switzerland	Meeting after the end of WP1 and WP2 to discuss their outcome and to plan the second part of the project.
25	1 week	3	Tanzania	Two people from CHUV will go to Tanzania for training of Tanzanian clinicians. The HEIG-VD PhD will also join the team to help with the software setup.

Risk management

Risk	Level	Mitigation
Computers of clinicians in the field are not powerful enough for the CDSS computations	Mid	We will rapidly develop a web front-end allowing the computations to be done remotely (a prototype of Tucuxi as a web application has just been developed and could be adapted to our needs). It would require an Internet access, but a slow data rate would be enough, as the amount of data to be transferred will be very low.
The HEIG-VD PhD student struggles with the modification of the core computing engine for IOV integration	Low	Yann Thoma has an in-depth understanding of the existing code base and will guide the development with the help of a software engineer from HEIG-VD that already worked on this project.
COVID-19 evolution prevents travels	Mid	A remote meeting will replace the kickoff in Tanzania. The same can apply to further in-person meetings if the COVID-19 situation requires it.
CDSS not validated by pharmacologists because of corner cases not handled correctly	Low	In such a case, we will add all the possible watchdogs within the software to let the clinician know that the CDSS could not handle their case as expected. In the medical field, we better have to conclude that the results are not relevant than to give wrong results. We would also add a third validation step after the last refactoring.
Not enough patients for getting samples at random times for PK model building	Low	Even with no such patients, the final model would be reasonably good. The more patients we have the better it will be, so we will delay by 2-3 months the model building to have time to contact other clinics.

Not enough patients/clinicians for the final prospective study	Low	The current contacts of KIDH should supply a sufficient number of participants. They will be contacted very in advance and if we require more participants, we will contact practitioners outside the KIDH network to enlarge the pool of clinicians at the time the study starts.
The ratio women-men in the cohorts of practitioners or patients is not reasonable (outside 40-60 or 60-40)	Mid	During the recruitment phase of clinicians and patients, when reaching 60% of people in a cohort, if an important discrepancy exists we will push towards a more selective approach for the remaining 40%.
CDSS recommendations not followed by clinicians during the implementation study	Mid	We will monitor the percentage of clinicians during the phases of the field implementation. If we see that more than 40% of clinicians are reluctant to follow CDSS recommendations without a plausible reason, strategies (such as additional intensive trainings, increasing expert support) will be developed to overcome this problem.

2.5 Relevance and impact

The TuberXpert project is a multidisciplinary research blending information technology, clinical expertise and modelling approaches to deploy precision pharmacotherapy of first line anti-TB medicine through dosage optimization in TB treatment.

Contribution to the field

Findings from this project will provide broad knowledge on the feasibility and appropriateness of dosage correction for individuals with sub-optimal drug exposure of medicinal drugs critical for the treatment of a life-threatening condition. The project will concretely validate a model-based dosage adjustment of rifampicin in TB patients. Through publications, it will enhance evidence-based information applicable in different countries.

Routine implementation of the TDM-CDSS particularly for rifampicin, which is a backbone for TB treatment, will transform the clinical management of TB. The current WHO rifampicin dosage of 10 mg/kg was designed rather empirically without prior evidence derived from pre-clinical or clinical trials [78]. Researchers have documented rifampicin sub-optimal drug levels in at least 50% or more of the TB treated population [14] [6]. However, there is limited evidence on utilization of technology to address the gaps [18]. This project will also improve the education of medical doctors in Tanzania concerning the dosage adjustment of rifampicin. The expertise will be made available in remote areas where there is a considerable number of TB patients.

Contributions to the patients care, disease management and public health

The project will contribute considerably to the END TB strategy through improving patients' treatment, particularly with arduous forms of TB (either with HIV co-infection or coexistent DM or malnutrition). It might definitely improve treatment outcomes of patients who would otherwise succumb or develop drug resistant TB as a result of sub-optimal drug exposure [79]. *A priori* dosage recommendations made in this project as a function of specific patient's characteristics will already limit the use of dangerous sub-therapeutic doses in these fragile populations. Furthermore, TDM can decrease the occurrence of adverse drug reactions in patients through favoring appropriate dosages and preventing overdoses [80]. This project challenges the *status quo* of empirical treatment towards individualization of therapeutics, a patient centered approach regarded as an important arsenal for the END TB strategy [81].

Contribution toward implementation of TDM-CDSS as an innovative technology

The TuberXpert project fosters collaborations of African/European countries that will enable Tanzania to produce high quality research on pharmacotherapy while strengthening research capacity, and Switzerland will benefit as well on innovation, science and entrepreneurship. The proof-of-concept will pave the way to a user-friendly TDM-CDSS that has good chances to prove applicable to other medicinal drugs.

Contribution towards the community of TDM users

At the end of the project, the source code of the CDSS and report generator will be publicly available, with a license allowing using it for non-profit purpose (possibility to use it for helping clinicians, but not to sell a software). If at some stage in the future a company is interested in commercializing a software embedding parts of the existing source code, a specific license with royalties will be considered as an option for a further closed-source exploitation. At the time of writing this proposal, the computing core of Tucuxi is not yet publicly available, but it will be by early 2022. The intent of HEIG-VD and CHUV is to offer access to the source code and the drug PK models to anyone interested in TDM. The result of TuberXpert will be proposed within this framework to help as many institutions and countries as possible. The vision is to build a community of institutions revolving around TDM, with participants from various countries able to take advantage of each other to improve the patient care. This will be of particular interest for African countries that could have access to such tools for free.

Expected publications and their potential target journals (either with gold Open Access or hybrid options)

- Algorithm and report layout for automated suggestions for rifampicin dosage adjustments (Health Informatics Journal)
- Literature review of existing rifampicin information relevant to TDM (British Journal of Clinical Pharmacology)
- Population pharmacokinetic models for rifampicin with emphasis on the Tanzanian population (Population Approach Group in Europe, PAGE, meeting presentations; Clinical Pharmacokinetics)
- Decision tree for helping practitioners with rifampicin dosage adjustment in the daily practice (Journal of Antimicrobial Chemotherapy)
- Clinical Decision Support System for rifampicin dosage adjustment (JMIR Medical Informatics)
- Generic *vs* drug-specific Clinical Decision Support System for individualized drug dosage adjustment (Therapeutic Drug Monitoring)
- Validation of a CDSS for rifampicin dosage adjustment by pharmacologists (Therapeutic Drug Monitoring)
- Implementation of a Clinical Decision Support System for Rifampicin TDM in Tanzania (JAC-antimicrobial resistance)
- Relationship between drug exposure and clinical outcomes to identify the best *a priori* dosage regimen strategy (Clinical Infectious Diseases)

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